METHODS OF ADMINISTERING OPIOID ANTAGONISTS AND COMPOSITIONS THEREOF

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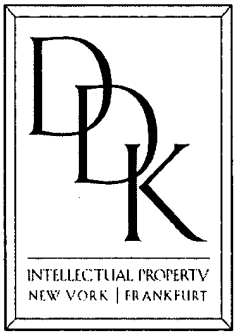

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METHODS OF ADMINISTERING OPIOID ANTAGONISTS AND COMPOSITIONS THEREOF

[0001] This application claims priority from U.S. Provisional Application No. 60/445,190, filed February 5, 2003, the disclosure of which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Opioid antagonists block or reverse effect of opioid agonists. One use of opioid antagonists is as a treatment to block euphoric effects that might be otherwise obtained upon administration of opioids to addicts. Another use of opioid antagonists has been to determine whether individuals are physically dependent on opioids. Still another use of opioid antagonists is to reverse the effects of opioids on individuals who have overdosed on opioid agonist drugs.

[0003] A particular opioid antagonist is naltrexone. The compound and methods for the synthesis of naltrexone are described in U.S. Patent No. 3,332,950.

[0004] The pharmacological and pharmacokinetic properties of naltrexone have been evaluated in multiple animal and clinical studies (see, e.g., Gonzalez J P, et al. Naltrexone: A review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy in the Management of Opioid Dependence, Drugs 1988; 35:192-213). Naltrexone is a synthetic congener of oxymorphone with negligible opioid agonist properties, i.e., some pupillary constriction has been reported in isolated cases. (see Gonzalez, 1988). The major effects of naltrexone are produced by the parent drug (17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one) and its primary metabolite (6-β-naltrexol) by binding competitively at opioid receptor sites within the central nervous system (primarily the brain), thus attenuating or completely blocking the agonistic effects of opioids.

[0005] Naltrexone has been reported to produce analgesia upon parenteral administration to mice (see Vaccarino et al., Analgesia Produced by Normal Doses of Opioid Antagonists Alone and in Combination with Morphine, Pain 1989; 36:103-109).

[0006] Following oral administration, naltrexone is rapidly absorbed (within 1 hour) and has an oral bioavailability ranging from 5-40%. Naltrexone's protein binding is approximately 21% and the volume of distribution following single-dose administration is 16.1 L/kg.

[0007] Naltrexone hydrochloride is commercially available in tablet form (Revia[7], DuPont) for the treatment of alcohol dependence and for the blockade of exogenously administered opioids (see, e.g., Revia, Physician's Desk Reference 51st ed.). A dosage of 50 mg Revia purportedly blocks the pharmacological effects of 25 mg IV administered heroin for up to 24 hours.

[0008] Another opioid antagonist is naloxone. Subcutaneous doses of up to 12 mg of naloxone produce no discernable subjective effects, and 24 mg naloxone causes only slight drowsiness. Small doses (0.4-0.8 mg) of naloxone given intramuscularly or intravenously in man prevent or promptly reverse the effects of morphine-like opioid agonist. One mg of naloxone intravenously has been reported to completely block the effect of 25 mg of heroin. The effects of naloxone are seen almost immediately after intravenous administration. The drug is absorbed after oral administration, but has been reported to be metabolized into an inactive form rapidly in its first passage through the liver such that it has been reported to be only one fiftieth as potent as when parenterally administered. Oral dosage of more than 1 g have been reported to be almost completely metabolized in less than 24 hours.

[0009] Other opioid antagonists include, for example, cyclazocine, nalmephene, cyclazocine, and levallorphan.

[0010] By virtue of the present invention, it has been surprisingly discovered that an opioid antagonist can be orally administered in an effective amount to provide analgesia. Such formulations and methods of treatment may have less abuse potential than formulations and methods for treating pain with conventional opioid agonists.

[0011] All documents cited herein, including the foregoing, are incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

[0012] It is an object of the invention to provide an oral dosage form for the treatment of pain and methods thereof.

[0013] It is an object of certain embodiments of the invention to provide an oral dosage form for the treatment of pain which is subject to less abuse than opioid agonist formulations.

[0014] It is an object of certain embodiments of the invention to provide an oral dosage form for the treatment of pain which is subject to less diversion than opioid agonist formulations.

[0015] It is an object of certain embodiments of the invention to provide a method of treating pain in a patient comprising orally administering an opioid antagonist in an effective amount to provide analgesia in a patient in need thereof.

[0016] It is an object of certain embodiments of the invention to provide a method of treating pain in a patient comprising diagnosing a patient to be in need of analgesia and orally administering to the patient an effective amount of an opioid antagonist to provide analgesia in the patient.

[0017] It is an object of certain embodiments of the invention to provide a method of treating pain in a patient comprising orally administering an opioid antagonist in an effective amount to provide analgesia in a patient in need thereof, wherein the patient is not alcohol dependent.

[0018] It is an object of certain embodiments of the invention to provide a method of treating pain in a patient comprising diagnosing a patient to be in need of analgesia and orally administering to the patient an effective amount of an opioid antagonist to provide analgesia in the patient, wherein the patient is not alcohol dependent.

[0019] It is an object of certain embodiments of the invention to provide a method of treating pain in a patient comprising orally administering an opioid antagonist in an effective amount to provide analgesia in a patient in need thereof, wherein the patient is not opioid dependent.

[0020] It is an object of certain embodiments of the invention to provide a method of treating pain in a patient comprising diagnosing a patient to be in need of analgesia and orally administering to the patient an effective amount of an opioid antagonist to provide analgesia in the patient, wherein the patient is not opioid dependent.

[0021] It is an object of certain embodiments of the invention to provide a method of treating pain in a patient comprising orally administering to the patient a pharmaceutical dosage form comprising an effective amount of an opioid antagonist (e.g., naltrexone hydrochloride) to provide analgesia in the patient; and a stabilizer which inhibits the formation of at least one degradation product of the opioid antagonist.

[0022] In certain embodiments, the invention is directed to an oral pharmaceutical composition comprising an analgesically effective amount of an opioid antagonist; and a sustained release carrier to provide a release of the opioid antagonist over a 12 to 24 hour period.

[0023] In certain embodiments, the invention is directed to an oral pharmaceutical composition comprising an active agent consisting essentially of an opioid antagonist; and a sustained release carrier to provide a release of the active agent over a 12 to 24 hour period.

[0024] In certain embodiments, the invention is directed to an oral pharmaceutical composition comprising an opioid antagonist and at least one non-opioid analgesic.

[0025] In certain embodiments, the invention is directed to an oral pharmaceutical composition comprising an active agent combination consisting essentially of an opioid antagonist and at least one non-opioid analgesic.

[0026] In certain embodiments, the invention is directed to an oral pharmaceutical composition comprising an opioid antagonist and at least one non-opioid analgesic, wherein the composition does not contain an opioid agonist.

[0027] In certain embodiments, the invention is directed to an oral pharmaceutical composition comprising an analgesically effective amount of an opioid antagonist (e.g. naltrexone hydrochloride); and a stabilizer which inhibits the formation of at least one degradation product of the opioid antagonist.

DETAILED DESCRIPTION OF THE INVENTION

[0028] Opioid antagonists, e.g., naltrexone, have been used in the treatment of opioid-induced toxicity, e.g., respiratory depression, in the diagnosis of physical dependence on opioids, and as therapeutic agents in the treatment of opioid abusers. All of these uses are a result of the antagonistic actions of the antgonist on opioid receptors. Naltrexone also has been reported to provide analgesia in mice upon parenteral administration. By virtue of the present invention, it has been surprisingly discovered that opioid antagonists, e.g., naltrexone, can be orally administered in an effective amount to induce analgesia, despite

having a poor oral bioavailability as compared to conventional orally administrable analgesics.

[0029] The methods and compositions of the present invention employ the opioid antagonist in a sufficient amount to provide analgesia to a patient upon oral administration. The amount can be from about 25 mg to about 150 mg, from about 25 mg to about 45 mg, or from about 55 mg to about 100 mg, depending on the clinical needs of the patient. These ranges are not meant to be limiting as one skilled in the art would understand that different patients may receive analgesia with higher or lower amounts. A skilled clinician would be able to determine the oral amount of antagonist required for analgesia on a patient-to-patient basis.

[0030] The opioid antagonists utilized in the present invention include, but are not limited to, naltrexone, naloxone, cyclazocine, nalmephene, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers thereof, esters thereof, and mixtures thereof. Naloxone and naltrexone are particularly preferred. The terms pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers thereof, and esters thereof are meant to mean those compounds which are analgesically effective.

[0031] The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, secium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparginate, glutamate and the like. When the antagonist is naltrexone, the hydrochloride salt is preferred.

[0032] In further embodiments, the methods and compositions of the present invention can include, in addition to the opioid antagonist, a non-opioid analgesic. Such non-opioid drugs would preferably provide additional analgesia, and include, for example, aspirin; acetaminophen; non-steroidal anti-inflammatory drugs ("NSAIDS"), e.g., ibuprofen, ketoprofen, etc.; N-methyl-D-aspartate (NMDA) receptor antagonists, e.g., a morphinan such as dextromethorphan or dextrorphan, or ketamine; cyclooxygenase-II inhibitors ("COX-II inhibitors"); and/or glycine receptor antagonists.

[0033] Suitable non-steroidal anti-inflammatory agents, include ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, pharmaceutically acceptable salts thereof, mixtures thereof, and the like. Useful dosages of these drugs are well known to those skilled in the art.

[0034] N-methyl-D-aspartate (NMDA) receptor antagonists are well known in the art, and encompass, for example, morphinans such as dextromethorphan or dextrorphan, ketamine, or pharmaceutically acceptable salts thereof. For purposes of the present invention, the term "NMDA antagonist" is also deemed to encompass drugs that at least partially inhibit a major intracellular consequence of NMDA-receptor activation, e.g. a ganglioside such as GM_1 or $GT_{1b,}$ a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(6-aminothexyl)-5-chloro-1-naphthalenesulfonamide. These drugs are stated to inhibit the development of tolerance to and/or dependence on addictive drugs, e.g., narcotic analgesics such as morphine, codeine, etc. in U.S. Patent Nos. 5,321,012 and 5,556,838 (both to Mayer, et al.), and to treat chronic pain in U.S. Patent No. 5,502,058 (Mayer, et al.). The NMDA antagonist may be included alone, or in combination with a local anesthetic such as lidocaine, as described in these Mayer, et al. patents.

[0035] The treatment of chronic pain via the use of glycine receptor antagonists and the identification of such drugs is described in U.S. Patent No. 5,514,680 (Weber, et al.).

[0036] COX-2 inhibitors have been reported in the art and many chemical structures are known to produce inhibition of cyclooxygenase-2. COX-2 inhibitors are described, for example, in U.S. Patent Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,475,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311. Certain preferred COX-2 inhibitors include celecoxib, 5-bromo-s-(4-fluorophenyl)-3-[4-(methylsufonyl)phenyl] thiophene, flosulide , meloxicam, rofecoxib , 6-methoxy-2 naphthylacetic acid , nabumetone, nimesulide, N-[2-(cyclohexyloxy)-4-nitrophenyl] methanesulfonamide, 1-fluoro-4-[2-[4-(methylsufonyl)phenyl]-1-cyclopenten-1-yl] benzene, 5-(4-fluorophenyl)-1-[4-(methylsufonyl)phenyl]-3-trifluoromethyl 1H-pyrazole, N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide, mixtures thereof, and pharmaceutically acceptable salts thereof. Dosage levels of COX-2 inhibitor are known in the art.

[0037] In yet further embodiments, a drug can be included which provides a desired effect other than analgesia, e.g., antitussive, anti-emetic, expectorant, decongestant, antihistamine drugs, local anesthetics, and the like.

[0038] In certain embodiments, the oral dosage forms of the present invention comprise an opioid antagonist combined with excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for oral administration which are known to the art. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical compositions can be sterilized and if desired mixed with auxiliary agents,

e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances.

[0039] The oral dosage forms of the present invention can be in the form of tablets, liquids, drops, gelcaps, troches, lozenges, aqueous or oily suspensions, multiparticulate formulations including dispersable powders, granules, pellets, matrix spheroids or coated inert beads, emulsions, hard or soft capsules or syrups or elixirs, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, etc.

[0040] The oral dosage forms may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. Such excipients include, for example, an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

[0041] Aqueous suspensions preferably contain the opioid antagonist in a mixture that has one or more excipients suitable as suspending agents, for example, pharmaceutically acceptable synthetic gums such as hydroxypropylmethylcellulose or natural gums. Oily suspensions may be formulated by suspending the above-identified combination of drugs in a vegetable oil or mineral oil. The oily suspensions may contain a thickening agent such as beeswax or cetyl alcohol. A syrup, elixir, or the like can be used, wherein a sweetened vehicle is employed.

[0042] The pharmaceutical oral compositions comprising an analgesically effective amount of opioid antagonist of the present invention can be prepared as immediate or sustained release formulations. For example, a sustained release carrier can be included

in the formulation to provide a release of the opioid antagonist over a 12 to 24 hour period.

[0043] In certain embodiments the oral dosage form includes a sustained-release material which is incorporated into a matrix along with the opioid antagonist to provide for the sustained release of the agent. The sustained-release material may be hydrophobic or hydrophilic as desired. The oral dosage form of the present invention may be prepared as granules, spheroids, matrix multiparticulates, etc. which comprise the opioid antagonist in a sustained release matrix, which may be compressed into a tablet or encapsulated. The oral dosage form of the present invention may optionally include other pharmaceutically acceptable ingredients (e.g., diluents, binders, colorants, lubricants, etc.).

[0044] In certain embodiments, the oral dosage form of the present invention may be an osmotic dosage form having a push or displacement composition as one of the layers of a bilayer core for pushing the opioid antagonist from the dosage form, and a semipermeable wall composition surrounding the core, wherein the wall has at least one exit means or passageway for delivering the opioid antagonist from the dosage form. Alternatively, the core of the osmotic dosage form may comprise a single layer core including a controlled release polymer and the opioid antagonist.

[0045] Preferably, the oral dosage forms of the present invention provide an analgesic effect for at least about 24 hours after administration.

SUSTAINED-RELEASE MATRIX FORMULATIONS

[0046] In one preferred embodiment of the present invention, the formulation can be a matrix with the opioid antagonist interdispersed in the sustained release carrier, to provide for the sustained release of the opioid antagonist.

[0047] A non-limiting list of suitable sustained-release materials which may be included in a sustained-release matrix according to the invention include hydrophilic and/or

hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials, waxes, shellac, and oils such as hydrogenated castor oil and hydrogenated vegetable oil. However, any pharmaceutically acceptable hydrophobic or hydrophilic sustained-release material which is capable of imparting sustained-release of the opioid antagonist may be used in accordance with the present invention. Preferred sustained-release polymers include alkylcelluloses such as ethylcellulose, acrylic and methacrylic acid polymers and copolymers; and cellulose ethers, especially hydroxyalkylcelluloses (especially hydroxypropylmethylcellulose) and carboxyalkylcelluloses. Preferred acrylic and methacrylic acid polymers and copolymers include methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, ethyl acrylate, trimethyl ammonioethyl methacrylate, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Certain preferred embodiments utilize mixtures of any of the foregoing sustained-release materials in the matrix of the invention.

[0048] The matrix also may include a binder. In such embodiments, the binder preferably contributes to the sustained-release of the opioid antagonist from the sustained-release matrix.

[0049] If an additional hydrophobic binder material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive. In certain preferred embodiments, a combination of two or more hydrophobic binder materials are included in the matrix formulations.

[0050] Preferred hydrophobic binder materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils, natural and synthetic waxes and polyalkylene glycols.

Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of the long-chain hydrocarbon binder materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 80% (by weight) of at least one digestible, long chain hydrocarbon.

[0051] In certain embodiments, the hydrophobic binder material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30 to about 100°C. In certain preferred embodiments, the dosage form comprises a sustained release matrix comprising the opioid antagonist and at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The hydroxyalkyl cellulose is preferably a hydroxy (C_1-C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form may be determined, inter alia, by the precise rate of opioid antagonist release required. The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the aliphatic alcohol in the present oral dosage form may be determined, as above, by the precise rate of opioid antagonist release required. It may also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between about 20% and about 50% (by wt) of the aliphatic alcohol. When a polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol and the

polyalkylene glycol preferably constitutes between about 20% and about 50% (by wt) of the total dosage form.

[0052] In one preferred embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the opioid antagonist from the formulation. In certain embodiments, a ratio of the hydroxyalkyl cellulose to the aliphatic alcohol/polyalkylene glycol of between 1:1 and 1:4 is preferred, with a ratio of between 1:2 and 1:3 being particularly preferred.

[0053] In certain embodiments, the polyalkylene glycol may be, for example, polypropylene glycol, or polyethylene glycol which is preferred. The average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000, especially between 1,500 and 12,000.

[0054] Another suitable sustained-release matrix comprises an alkylcellulose (especially ethylcellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

[0055] In addition to the above ingredients, a sustained-release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

[0056] In order to facilitate the preparation of a solid, sustained-release oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, sustained-release oral dosage form according to the present invention comprising incorporating the opioid antagonist in a sustained-release matrix. Incorporation in the matrix may be effected, for example, by:

(a) forming granules comprising at least one hydrophobic and/or hydrophilic material as set forth above (e.g., a water soluble hydroxyalkyl cellulose) together with the opioid antagonist;

(b) mixing the granules containing at least one hydrophobic and/or hydrophilic material with at least one C_{12}-C_{36} aliphatic alcohol, and

(c) optionally, compressing and shaping the granules.

[0056] The granules may be formed by any of the procedures well-known to those skilled in the art of pharmaceutical formulation. For example, in one preferred method, the granules may be formed by wet granulating hydroxyalkyl cellulose/opioid antagonist with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the opioid antagonist.

[0057] A sustained-release matrix can also be prepared by, e.g., melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic binder material, e.g., a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate a hydrophobic sustained-release material, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic binder material. Examples of sustained-release formulations prepared via melt-granulation techniques are found, e.g., in U.S. Patent No. 4,861,598.

[0058] The additional hydrophobic binder material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve sustained release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like binder substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

[0059] The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the opioid antagonist, together

with a sustained release material and preferably a binder material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded, e.g., using a twin-screw extruder, to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The matrix multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the opioid antagonist for a time period of at least about 24 hours.

[0060] An optional process for preparing the melt extruded formulations of the present invention includes directly metering into an extruder a hydrophobic sustained release material, the opioid antagonist, and an optional binder material; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into matrix multiparticulates having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

[0061] Plasticizers, such as those described above, may be included in melt-extruded matrices. The plasticizer is preferably included as from about 0.1 to about 30% by weight of the matrix. Other pharmaceutical excipients, e.g., talc, mono or poly saccharides, colorants, flavorants, lubricants and the like may be included in the sustained release matrices of the present invention as desired. The amounts included will depend upon the desired characteristic to be achieved.

[0062] The diameter of the extruder aperture or exit port can be adjusted to vary the thickness of the extruded strands. Furthermore, the exit port of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

[0063] A melt extruded matrix multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit port. For purposes of the present invention, the terms "melt-extruded matrix multiparticulate(s)" and "melt-extruded matrix multiparticulate system(s)" and "melt-extruded matrix particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic sustained release material as described herein. Preferably the melt-extruded matrix multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded matrix multiparticulates can be any geometrical shape within this size range. In certain embodiments, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

[0064] In one preferred embodiment, oral dosage forms are prepared that include an effective amount of melt-extruded matrix multiparticulates within a capsule. For example, a plurality of the melt-extruded matrix multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastrointestinal fluid.

[0065] In another embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).

[0066] In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Patent No. 4,957,681 (Klimesch, et. al.).

[0067] Optionally, the sustained-release matrix multiparticulate systems, tablets, or capsules can be coated with a sustained release coating such as the sustained release

coatings described herein. Such coatings preferably include a sufficient amount of hydrophobic and/or hydrophilic sustained-release material to obtain a weight gain level from about 2 to about 25 percent, although the overcoat may be greater depending upon, e.g., the desired release rate.

[0068] Sustained release dosage forms of the present invention may further include an amount of an immediate release therapeutically active opioid antagonist for prompt therapeutic effect. The immediate release opioid antagonist may be incorporated, e.g., as separate multiparticulates within a gelatin capsule, or may be coated on the surface of, e.g., melt extruded matrix multiparticulates.

[0069] The sustained-release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of sustained-release material, by varying the amount of plasticizer relative to other matrix constituents, by varying the amount of hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

[0070] In other embodiments of the invention, melt-extruded formulations are prepared without the inclusion of the opioid antagonist, which is added thereafter to the extrudate. Such formulations typically will have the opioid antagonist blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the therapeutically active agent included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

[0071] Typical melt-extrusion production systems suitable for use in accordance with the present invention include a suitable extruder drive motor having variable speed and constant torque control, start-stop controls, and a meter. In addition, the production system will include a temperature control console which includes temperature sensors, cooling means and temperature indicators throughout the length of the extruder. In addition, the production system will include an extruder such as a twin-screw extruder

which consists of two counter-rotating intermeshing screws enclosed within a cylinder or barrel having an aperture or die at the exit thereof. The feed materials enter through a feed hopper and are moved through the barrel by the screws and are forced through the die into strands which are thereafter conveyed such as by a continuous movable belt to allow for cooling and being directed to a pelletizer or other suitable device to render the extruded ropes into the matrix multiparticulate system. The pelletizer can consist of rollers, fixed knife, rotating cutter and the like. Suitable instruments and systems are available from distributors such as C.W. Brabender Instruments, Inc. of South Hackensack, New Jersey. Other suitable apparatus will be apparent to those of ordinary skill in the art.

[0072] Alternatively, the melt-extruded product is prepared using a Werner-Pfleiderer twin screw extruder.

[0073] In certain embodiments, a spheronizing agent is added to a granulate or matrix multiparticulate and then spheronized to produce sustained release spheroids. The spheroids are then optionally overcoated with a sustained release coating by methods such as those described above.

[0074] Spheronizing agents which may be used to prepare the matrix multiparticulate formulations of the present invention include any art-known spheronizing agent. Cellulose derivatives are preferred, and microcrystalline cellulose is especially preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (TradeMark, FMC Corporation). The spheronizing agent is preferably included as about 1 to about 99% of the matrix multiparticulate by weight.

[0075] In certain embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble

polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose.

[0076] In certain embodiments, a sustained release coating is applied to the sustained release spheroids, granules, or matrix multiparticulates. In such embodiments, the sustained-release coating may include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein. The coating is preferably derived from an aqueous dispersion of the hydrophobic sustained release material.

[0077] In certain embodiments, it is necessary to overcoat the sustained release spheroids, granules, or matrix multiparticulates comprising the opioid antagonist and sustained release carrier with a sufficient amount of the aqueous dispersion of, e.g., alkylcellulose or acrylic polymer, to obtain a weight gain level from about 2 to about 50%, e.g., about 2 to about 25%, in order to obtain a sustained-release formulation. The overcoat may be lesser or greater depending upon, e.g., the desired release rate, the inclusion of plasticizer in the aqueous dispersion and the manner of incorporation of the same. Cellulosic materials and polymers, including alkylcelluloses, are sustained release materials well suited for coating the sustained release spheroids, granules, or matrix multiparticulates according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

[0078] One commercially–available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pennsylvania, U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water–immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the

manufacturing phase. Thus, prior to using the same as a coating, it is necessary to mix the Aquacoat® with a suitable plasticizer prior to use.

[0079] Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pennsylvania, U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly to the sustained release spheroids, granules, or matrix multiparticulates.

[0080] In other preferred embodiments of the present invention, the sustained release material comprising the sustained-release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[0081] In addition to the above ingredients, the spheroids, granules, or matrix multiparticulates may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the formulation if desired. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

[0082] Specific examples of orally acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

[0083] It has further been found that the addition of a small amount of talc to the sustained release coating reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

PROCESSES FOR PREPARING MATRIX BEADS

[0084] Controlled-release dosage forms according to the present invention may also be prepared as matrix bead formulations. The matrix beads include a spheronising agent and the opioid antagonist.

[0085] The opioid antagonist preferably comprises from about 0.01 to about 99 % by weight of the matrix bead by weight. It is preferable that the opioid antagonist is included as about 0.1 to about 50 % by weight of the matrix bead.

[0086] Spheronising agents which may be used to prepare the matrix bead formulations of the present invention include any art-known spheronising agent. Cellulose derivatives are preferred, and microcrystalline cellulose is especially preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). The spheronising agent is preferably included as about 1 to about 99% of the matrix bead by weight.

[0087] In addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkylcellulose, such as hydroxypropylcellulose, are preferred.

[0088] In addition to the opioid antagonist and spheronising agent, the matrix bead formulations of the present invention may include a controlled release material such as those described hereinabove. Preferred controlled-release materials for inclusion in the matrix bead formulations include acrylic and methacrylic acid polymers or copolymers, and ethylcellulose. When present in the formulation, the controlled-release material will

be included in amounts of from about 1 to about 80% of the matrix bead, by weight. The controlled-release material is preferably included in the matrix bead formulation in an amount effective to provide controlled release of the opioid antagonist from the bead.

[0089] Pharmaceutical processing aids such as binders, diluents, and the like may be included in the matrix bead formulations. Amounts of these agents included in the formulations will vary with the desired effect to be exhibited by the formulation.

[0090] The matrix beads may be overcoated with a controlled-release coating including a controlled-release material such as those described hereinabove. The controlled-release coating can be applied to a weight gain of from about 5 to about 30 %. The amount of the controlled-release coating to be applied will vary according to a variety of factors, e.g., the composition of the matrix beads.

[0091] Matrix beads are generally prepared by granulating the spheronising agent together with the agent, e.g. by wet granulation. The granulate is then spheronized to produce the matrix beads. The matrix beads are then optionally overcoated with the controlled release coating by methods such as those described hereinabove.

[0092] Another method for preparing matrix beads comprises, for example, (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and an opioid antagonist; (b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12} - C_{36} aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/nalterexone with water.

[0093] In yet other alternative embodiments, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder.

Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained-release coating will generally include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

CONTROLLED RELEASE BEAD FORMULATIONS

[0094] In one especially preferred embodiment, the oral dosage form comprises an effective number of controlled release spheroids contained within a gelatin capsule.

[0095] In another preferred embodiment of the present invention, the controlled-release dosage form comprises spheroids containing the active ingredient coated with a controlled-release coating including a controlled release material. The term spheroid is known in the pharmaceutical art and means, e.g., a spherical granule having a diameter of between 0.1 mm and 2.5 mm, or between 0.5 mm and 2 mm. This range is not meant to be limiting as the diameter can be higher or lower than disclosed above.

[0096] The spheroids can be film coated with a controlled release material that permits release of the opioid antagonist at a controlled rate in an aqueous medium. The film coat can be chosen so as to achieve a desired in-vitro release rate. The controlled-release coating formulations of the present invention preferably produce a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non–toxic, inert, and tack–free.

COATINGS

[0097] The oral dosage forms of the present invention may optionally be coated with one or more coatings suitable for the regulation of release or for the protection of the

formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal (GI) fluid. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. Other preferred embodiments include a pH-dependent coating that releases the opioid antagonist in desired areas of the GI tract, e.g., the stomach or small intestine. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

[0098] Formulations according to the invention that utilize pH-dependent coatings may also impart a repeat-action effect whereby unprotected drug is coated over an enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include a controlled release material such as, e.g., shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

[0099] In another preferred embodiment, the present invention is related to a stabilized solid controlled dosage form comprising the opioid antagonist coated with a hydrophobic controlled release material selected from (i) an alkylcellulose; (ii) an acrylic polymer; and (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion.

[0100] In certain preferred embodiments, the controlled release coating is derived from an aqueous dispersion of the hydrophobic controlled release material. The coated substrate containing the opioid antagonist (e.g., a tablet core or inert pharmaceutical beads or spheroids) is then cured until an endpoint is reached at which the substrate provides a stable dissolution. The curing endpoint may be determined by comparing the dissolution profile (curve) of the dosage form immediately after curing to the dissolution

profile (curve) of the dosage form after exposure to accelerated storage conditions of, e.g., at least one month at a temperature of 40°C and a relative humidity of 75%. These formulations are described in detail in U.S. Patent Nos. 5,273,760 and 5,286,493. Other examples of controlled-release formulations and coatings which may be used in accordance with the present invention include those described in U.S. Patent Nos. 5,324,351; 5,356,467; and 5,472,712.

[0101] In preferred embodiments, the controlled release coatings include a plasticizer such as those described herein below.

[0102] In certain embodiments, it is necessary to overcoat the substrate comprising the opioid antagonist with a sufficient amount of the aqueous dispersion of e.g., alkylcellulose or acrylic polymer, to obtain a weight gain level from about 2 to about 50%, e.g., about 2 to about 25% in order to obtain a controlled-release formulation. The overcoat may be lesser or greater depending upon the physical properties of the therapeutically active agent and the desired release rate, the inclusion of plasticizer in the aqueous dispersion and the manner of incorporation of the same, for example.

ALKYLCELLULOSE POLYMERS

[0103] Cellulosic materials and polymers, including alkylcelluloses are controlled release materials well suited for coating the substrates, e.g., beads, tablets, etc. according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coatings according to the invention.

[0104] One commercially–available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pennsylvania, U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water–immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate

submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

[0105] Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pennsylvania, U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

ACRYLIC POLYMERS

[0106] In other preferred embodiments of the present invention, the controlled release material comprising the controlled-release coating is a pharmaceutically acceptable acrylic polymer selected from, but not limited to, acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[0107] In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

[0108] In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical

properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

[0109] Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm Tech, Inc. There are several different types of Eudragit®. For example, Eudragit E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit L is a methacrylic acid copolymer which does not swell at about pH < 5.7 and is soluble at about pH > 6. Eudragit S does not swell at about pH < 6.5 and is soluble at about pH > 7. Eudragit RL and Eudragit RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit RL and RS are pH-independent.

[0110] In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

[0111] The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a controlled-release formulation having a desirable dissolution profile. Desirable controlled-release formulations may be obtained,

for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL:Eudragit® 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

PLASTICIZERS

[0112] In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic controlled release material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the controlled-release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing controlled-release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

[0113] Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tibutyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

[0114] Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2–propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic

films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

[0115] It has further been found that the addition of a small amount of talc to the controlled release coating reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

PREPARATION OF COATED BEAD FORMULATIONS

[0116] When an aqueous dispersion of hydrophobic material is used to coat substrates, e.g., inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant stabilized solid controlled-release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled-release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

[0117] The stabilized controlled-release bead formulations of the present invention slowly release the opioid antagonist, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled-release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic controlled release material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic controlled release material, by varying the amount of plasticizer relative to hydrophobic controlled release material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the controlled release coating.

[0118] Substrates coated with a therapeutically active agent are prepared, e.g. by dissolving the therapeutically active agent in water and then spraying the solution onto a

substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the opioid antagonist to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropyl methylcellulose, etc. with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the substrate. The resultant coated substrate may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled-release coating.

[0119] An example of a suitable barrier agent is one which comprises hydroxypropyl methylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

[0120] The substrates may then be overcoated with an aqueous dispersion of the hydrophobic controlled release material. The aqueous dispersion of hydrophobic controlled release material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat® or Surelease®, may be used. If Surelease® is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit® can be used.

[0121] The coating solutions of the present invention preferably contain, in addition to the film–former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color can be added to Aquacoat® via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat®. Alternatively, any suitable method of providing color to the formulations of the present invention may be

used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

[0122] The plasticized aqueous dispersion of hydrophobic controlled release material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized–bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the aqueous dispersion of hydrophobic material to obtain a predetermined controlled-release of said therapeutically active agent when said coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic controlled release material, a further overcoat of a film-former, such as Opadry®, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

[0123] The release of the therapeutically active agent from the controlled-release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic controlled release material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

[0124] The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

[0125] The controlled-release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

[0126] The controlled-release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

[0127] The release-modifying agent may also comprise a semi-permeable polymer. In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

[0128] The controlled-release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Patent Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864. The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

[0129] Another method of producing controlled release bead formulations suitable for about 24-hour administration is via powder layering. U.S. Patent No. 5,411,745 teaches preparation of 24-hour morphine formulations prepared via powder layering techniques utilizing a processing aid consisting essentially of hydrous lactose impalpable. The powder-layered beads are prepared by spraying an aqueous binder solution onto inert beads to provide a tacky surface, and subsequently spraying a powder that is a homogenous mixture of morphine sulfate and hydrous lactose impalpable onto the tacky beads. The beads are then dried and coated with a hydrophobic material such as those described hereinabove to obtain the desired release of drug when the final formulation is exposed to environmental fluids. An appropriate amount of the controlled release beads are then, e.g., encapsulated to provide a final dosage form which provides effective plasma concentrations of morphine for about 24 hours.

SUSTAINED RELEASE OSMOTIC DOSAGE

[0130] Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

[0131] The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, or porous element through which the opioid antagonist can be pumped, diffuse or migrate through a fiber, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The passageway can have any shape, such as round, triangular, square and elliptical, for assisting in the sustained metered release of opioid antagonist from the dosage form. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Patent Nos. 3,845,770; 3,916,899; 4,063,064 and 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are disclosed in U.S. Patent Nos. 4,200,098 and 4,285,987.

[0132] In certain embodiments, the bilayer core comprises a drug layer with the opioid antagonist and a displacement or push layer. In certain embodiments the drug layer may

also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6\ H_{12}\ O_5)_n \cdot H_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

[0133] In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethylcellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form,

thereby swelling and expanding as an osmotic hydrogel (also known as osmogel), whereby they push the opioid antagonist from the osmotic dosage form.

[0134] The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulfate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulfate, sodium sulfate, potassium phosphate, glucose, fructose and maltose.

[0135] The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkylcellulose is represented by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

[0136] The push layer optionally may comprise a nontoxic colorant or dye. Examples of colorants or dyes include but are not limited to Food and Drug Administration Colorant (FD&C), such as FD&C No. 1 blue dye, FD&C No. 4 red dye, red ferric oxide, yellow ferric oxide, titanium dioxide, carbon black, and indigo.

[0137] The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium

bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphatocopherol, and propylgallate.

[0138] In certain alternative embodiments, the dosage form comprises a homogenous core comprising the opioid antagonist, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc.). The homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the opioid antagonist.

[0139] In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkinylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

[0140] Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethycellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Patent Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Patent No. 3,133,132; semipermeable crosslinked polystyrenes; semipermeable cross-linked poly(sodium styrene sulfonate); semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride); and semipermeable polymers possessing a fluid permeability of $2.5x10^{-8}$ to $2.5x10^{-2}$ (cm^2 /hr·atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present invention are known in the

art in U.S. Patent Nos. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

[0141] In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laureate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

[0142] In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

[0143] In certain preferred embodiments, the present invention includes a therapeutic composition comprising 1 to 640 mg of the opioid antagonist, 25 to 500 mg of poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 to 50 mg of poly(vinylpyrrolidone) having a 40,000 average molecular weight, and 0 to about 7.5 mg of a lubricant.

[0144] In certain embodiments, the invention also provides a method for administering an opioid antagonist by admitting orally a dosage form comprising 1 to 640 mg of an opioid antagonist, a semipermeable wall permeable to aqueous-biological fluid and

impervious to the passageway of the opioid antagonist, which semipermeable wall surrounds an internal space comprising the opioid antagonist composition and a push composition, the opioid antagonist composition comprising 1 to 640 mg of opioid antagonist, 25 to 500 mg of a poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 to 50 mg of a poly(vinylpyrrolidone) having a 40,000 average molecular weight, and 0 to 7.5 mg of a lubricant, said push composition comprising 15 to 250 mg of a poly(alkylene oxide) of 3,000,000 to 7,500,000 average molecular weight, 0 to 75 mg of an osmagent, 1 to 50 mg of a hydroxyalkylcellulose, 0 to 10 mg of ferric oxide, 0 to 10 mg of a lubricant, and 0 to 10 mg of antioxidant; and a passageway in the semipermeable wall for delivering the opioid antagonist from the dosage form, by imbibing fluid through the semipermeable wall into the dosage form causing the opioid antagonist composition to become dispensable and the push composition to expand and push the opioid antagonist composition through the passageway, whereby through the combined operations of the dosage form, the opioid antagonist is delivered at a therapeutically effective dose at a rate controlled over a sustained period of time.

[0145] The dosage forms of the present invention may optionally be coated with one or more coatings suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal (GI) fluid. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. Other preferred embodiments include a pH-dependent coating that releases the opioid antagonist in desired areas of the GI tract, e.g., the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about twelve hours and preferably about twenty-four hours or more of analgesia to a patient. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

[0146] Formulations according to the invention that utilize pH-dependent coatings may also impart a repeat-action effect whereby unprotected drug is coated over an enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent and may be used in accordance with the present invention include a sustained release material such as, e.g., shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

[0147] In certain embodiments of the present invention, an effective amount of opioid antagonist in immediate release form is included in the formulation. By including such an effective amount of immediate release opioid antagonist in the unit dose, the experience of relatively higher levels of pain in patients may be reduced. In such embodiments, an effective amount of the opioid antagonist in immediate release form may be coated onto the tablet of the present invention. For example, where the extended release of the opioid antagonist from the formulation is due to a sustained release coating, the immediate release layer would be overcoated on top of the sustained release coating. On the other hand, the immediate release layer may be coated onto the surface of tablets wherein the opioid antagonist is incorporated in a sustained release matrix. One skilled in the art would recognize still other alternative manners of incorporating the immediate release opioid antagonist portion into the formulation. Such alternatives are deemed to be encompassed by the appended claims.

[0148] The additional (non-opioid) therapeutically active agent may be included in sustained release form or in immediate release form. The additional drug may be incorporated into the sustained release matrix along with the opioid antagonist, may be incorporated as a powder, granulation, etc. into the dosage form, or may be incorporated as a separated sustained release layer or immediate release layer.

[0149] The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1 (Prophetic)

[0150] Sustained Release Naltrexone hydrochloride formulations are prepared with the formula in Table 1 below:

TABLE 1

Ingredients	Amt/Unit (mg)
Naltrexone HCl	45.0
Spray Dried Lactose	59.25
Povidone	5.0
Eudragit RS30D (solids)	10.0
Triacetin	2.0
Stearyl Alcohol	25.0
Talc	2.5
Magnesium Stearate	1.25
Opadry Pink Y-S-14518A	5.0
Total	135.95

1. Dispersion: Naltrexone HCl is dissolved in water and the solution is added to a Eudragit/Triacetin dispersion.

2. Granulation: Spray the Eudragit/Triacetin dispersion onto the Spray Dried Lactose and Povidone using a fluid bed granulator.

3. Milling: Discharge the granulation and pass through a mill with approximately 1 mm openings (18 mesh screen).

4. Waxing: Melt the stearyl alcohol at about 50 degrees C and add to the milled granulation using a high shear mixer. Allow to cool at room temperature on trays or a fluid bed.

5. Milling: Pass the cooled granulation through a mill with approximately 18 mesh screen.

6. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.

7. Compression: Compress the granulation into tablets using a Kilian® tablet press.

8. Film Coating: Apply an aqueous film coat to the tablets using a rotary pan.